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Evaluation of Preload Reserve During Isometric Exercise Testing in Patients With Old Myocardial Infarction: Doppler Echocardiographic Study

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To estimate the preload reserve in response to an increase in afterload in patients with old myocardial infarction, the relation between the Doppler echocardiographic inflow velocity pattern and left ventricular end-diastolic pressure was investigated during isometric handgrip exercise testing. The study population consisted of 16 normal subjects and 40 patients with old myocardial infarction. The 40 patients were subdivided into two groups according to left ventricular end-diastolic pressure at rest: group I (22 patients), less than 18 mm Hg; group II (18 patients), 18 mm Hg or more.

At rest, the ratio of peak velocity in atrial contraction phase to peak velocity in early diastolic filling phase (A/E) was significantly higher in the patients with old myocardial infarction than in normal subjects; values in the two subgroups of myocardial infarction did not differ significantly. The A/E ratio and left ventricular end-diastolic pressure increased significantly during exercise in group I. Conversely, the change in left ventricular end-diastolic pressure during exercise in group II was significantly greater than that in group I, and was associated with a decrease in the A/E ratio.

Thus, an atrial compensatory mechanism operated effectively in response to the increase in afterload in patients with a normal left ventricular filling pressure, whereas this compensatory mechanism deteriorated in patients with elevated left ventricular filling pressure due to a limited preload reserve.

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The transmitral inflow velocity pattern obtained by pulsed Doppler echocardiography has been used recently to assess left ventricular diastolic function (1–6). Impaired left ventricular diastolic filling properties have been reported (7–12) in patients with coronary artery disease, even in the absence of evidence of deterioration of left ventricular systolic function. Although left ventricular end-diastolic pressure is a clinically useful index of preload, it can be determined only by invasive techniques. Investigators (13–15) recently attempted to estimate this variable noninvasively by comparing the Doppler-determined inflow velocity pattern with left ventricular filling pressure obtained at cardiac catheterization. However, this pattern is influenced by many hemodynamic factors, such as afterload, left atrial filling pressure, myocardial stiffness and chamber stiffness (1,14,16–18). Therefore, it may not be adequate to estimate preload by evaluating the velocity pattern only at one point.

In this study, the relation between changes in the left ventricular inflow velocity pattern and left ventricular end-diastolic pressure was investigated during isometric handgrip exercise testing to estimate noninvasively the preload reserve in response to an acute increase in afterload in patients with old myocardial infarction.

Methods

Study patients. The study population consisted of 16 normal volunteers (10 men and 6 women, mean age 51 ± 9 years) and 40 patients with old myocardial infarction (30 men and 10 women, mean age 57 ± 8 years). Normal volunteers were recruited from among members of the hospital staff who had 1) a normal medical history, 2) normal physical examination, chest radiograph and echocardiogram and 3) negative exercise test.

Forty patients with a history of myocardial infarction underwent catheterization for evaluation of cardiac function and coronary artery lesions, and all were found to have coronary artery obstruction with left ventricular wall motion abnormalities. None of the patients had post-infarction angina. The 40 patients were subdivided into two groups according to the left ventricular end-diastolic pressure at rest: group I, less than 18 mm Hg (22 patients, mean age 58 ± 8 years) and group II, 18 mm Hg or more (18 patients, mean age 56 ± 9 years). All patients were in sinus rhythm. Patients with diabetes mellitus and moderate or severe mitral regurgitation on color Doppler echocardiography were ex-

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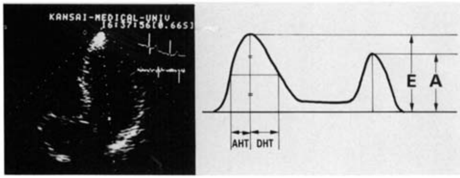

Figure 1. Variables derived from the transmitral inflow velocity pattern. Peak velocity in the early diastolic filling phase (E), peak velocity in the atrial contraction phase (A) and their ratio (A/E) and acceleration half-time (AHT) and deceleration half-time (DHT) of the rapid filling phase are obtained. AHT and DHT are corrected by heart rate ($/\sqrt{R\text{-}R}$).

cluded from this study. No patient had a history of hypertension or evidence of left ventricular hypertrophy on echocardiography. Use of all cardiac medications was discontinued for at least 48 hours before the study. All patients gave written, informed consent before the study. The study protocol was approved by the Kansai Medical University Committee of Human Research.

Pulsed Doppler echocardiographic studies (Fig. 1). An Aloka SSD 880 or 870 ultrasound color Doppler system was used. The measurements of transmitral inflow were performed from the apical four-chamber view. With the guidance of a real-time two-dimensional color Doppler flow image, the Doppler sample volume was placed at the level of the mitral anulus and the position was then adjusted so as to direct the ultrasound beam parallel to left ventricular inflow. Flow velocity curves were recorded for at least three cardiac cycles on a strip chart at a paper speed of 100 mm/s. Left ventricular filling velocity was characterized by a biphasic pattern including the early diastolic filling phase (E wave) and the late atrial contraction phase (A wave). Peak velocity of the E wave (cm/s) and A wave (cm/s) and their ratio (A/E) were measured. The acceleration half-time/ $\sqrt{R\text{-}R}$ (ms) and deceleration half-time/ $\sqrt{R\text{-}R}$ (ms) of the E wave were also obtained.

Isometric handgrip exercise. After 20 min of rest in the supine position, each subject performed the prescribed isometric exercise test using a handgrip dynamometer, which was held at 50% of the maximal voluntary contraction for 2 minutes. The left ventricular filling velocity pattern, systolic blood pressure, diastolic blood pressure, heart rate and pressure-rate product were measured at rest and during exercise.

Cardiac catheterization. The 40 patients with old myocardial infarction underwent cardiac catheterization using the Judkins technique within 24 hours (mean 21 ± 2) after the pulsed Doppler echocardiographic examination. Left ventricular end-diastolic pressure was measured using a fluid-filled catheter before coronary angiography and left ventriculography. Left ventricular end-diastolic pressure was taken as the point that followed the A wave at which left ventricular pressure increased sharply. Left ventricular end-diastolic pressure at rest was measured in all 40 patients, and in 14 of them it was also measured during isometric exercise.

Statistical analysis. Analysis of variance and Scheffe's method were used to assess the differences among the three groups. A Student t test was used to compare two patient groups and a paired t test for paired samples. Statistical significance was accepted at the 95% confidence level ($p < 0.05$). Linear regression analysis was performed by the least-squares method. Values are given as mean ± SD.

Table 1. Changes in Heart Rate, Blood Pressure and Pressure-Rate Product During Exercise

		N* (n = 16)	I† (n = 22)	II‡ (n = 18)	F Value
HR (beats/min)	R	64 ± 5	63 ± 10	66 ± 9	0.49 NS
	E	72 ± 6	69 ± 14	74 ± 11	1.21 NS
p value (R vs E)		<0.001	<0.01	<0.01	
SBP (mm Hg)	R	113 ± 12	124 ± 20	117 ± 14	2.24 NS
	E	146 ± 12	153 ± 25	141 ± 23	1.63 NS
p value (R vs E)		<0.001	<0.01	<0.01	
DBP (mm Hg)	R	79 ± 10	81 ± 8	79 ± 9	0.26 NS
	E	99 ± 8	98 ± 11	94 ± 14	0.74 NS
p value (R vs E)		<0.001	<0.01	<0.01	
PRP ($\times 10^2$ mm Hg/min)	R	68 ± 21	78 ± 15	76 ± 14	0.24 NS
	E	106 ± 13	105 ± 26	104 ± 21	0.02 NS
p value (R vs E)		<0.001	<0.01	<0.01	

N = normal subjects; I = patients with old myocardial infarction and rest left ventricular end-diastolic pressure <18 mm Hg; II = patients with old myocardial infarction and rest left ventricular end-diastolic pressure ≥18 mm Hg. DBP = diastolic blood pressure; E = exercise; HR = heart rate; PRP = pressure-rate product; R = rest; SBP = systolic blood pressure.

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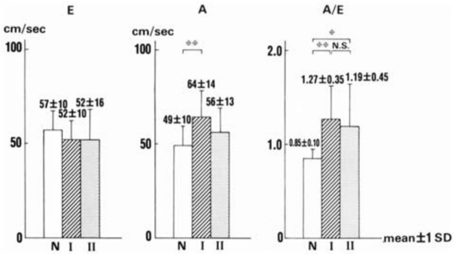


Figure 2. Comparison of peak velocity in early diastolic filling phase (E), peak velocity in atrial contraction phase (A) and their ratio (A/E) at rest in the three groups. The A/E ratio in groups I and II is greater than that of normal subjects (N), but there are no significant differences (N.S.) between the two groups with old myocardial infarction. *p < 0.05. **p < 0.01.

Results

In none of the patients did exercise-induced chest pain, ST-T changes or arrhythmia develop during handgrip exercise.

Heart rate and blood pressure response during isometric handgrip exercise (Table 1). Heart rate, blood pressure and pressure-rate product at rest did not differ significantly among the three groups. Values for all three indexes increased significantly during exercise, with no significant differences observed among the three groups at 2 min of exercise.

Doppler flow measurements at rest (Fig. 2). The A/E ratio was significantly higher in both groups with old myocardial infarction than in the normal subjects; values did not differ significantly between the two subgroups of myocardial infarction. Acceleration half-time/ $\sqrt{R\text{-}R}$, deceleration half-time/ $\sqrt{R\text{-}R}$ and acceleration half-time/ $\sqrt{R\text{-}R}$ + deceleration half-time/ $\sqrt{R\text{-}R}$ did not differ significantly among the three groups.

Response of Doppler flow measurements during isometric handgrip exercise (Fig. 3, 4 and 5). Peak velocity of the E wave did not change significantly, but that of the A wave and the A/E ratio increased significantly during exercise in the normal subjects. Peak velocity of the E wave decreased significantly, whereas that of the A wave and the A/E ratio increased significantly during exercise in group I. In group II, peak velocity of the E wave increased significantly, peak velocity of the A wave decreased in 14 of 18 patients and the A/E ratio decreased significantly during exercise. As a result, the A/E ratio in group I was significantly higher than that in the normal group and group II at 2 min of exercise. The change in A/E ratio in group I was significantly greater than that in the other two groups, whereas the change in group II showed a negative value that was significantly smaller than that in the other two groups. Acceleration half-time/ $\sqrt{R\text{-}R}$ + the deceleration half-time/ $\sqrt{R\text{-}R}$ did not change during exercise in the normal group (4.7 ± 0.4 to 4.6 ± 0.6 ms) or in group I (5.1 ± 0.9 to 5.2 ± 0.9 ms), but shortened significantly (4.7 ± 0.7 to 4.2 ± 0.8 ms) during exercise in group II ($p < 0.01$).

A/E and left ventricular end-diastolic pressure (Fig. 6 and 7). In group I, heart rate and blood pressure at rest during cardiac catheterization were 64 ± 8 beats/min and 123 ± 15/80 ± 8 mm Hg, respectively, and in group II they were 66 ± 8 beats/min and 118 ± 10/80 ± 10 mm Hg. Heart rate and blood pressure at rest did not differ in the two subgroups at the time of Doppler examination and cardiac catheterization (Table 1). There was no significant correlation between

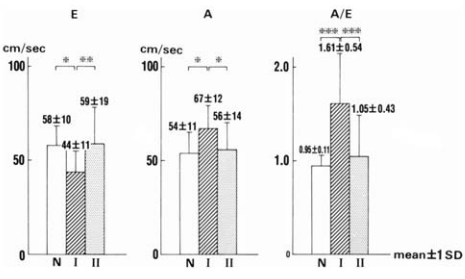


Figure 3. Comparison of peak velocity in early diastolic filling phase (E), peak velocity in atrial contraction phase (A) and their ratio (A/E) among the three groups at 2 min of exercise. The A/E ratio in group I is significantly higher than that in the other two groups. *p < 0.05. **p < 0.01. ***p < 0.001.

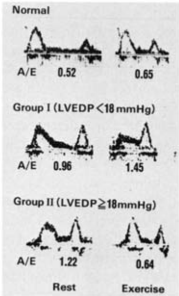
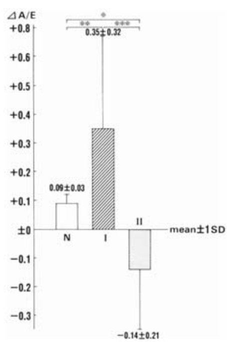


Figure 4. Response of the transmitral inflow velocity pattern during exercise. The ratio of peak velocity in atrial contraction phase to peak velocity in early diastolic filling phase (A/E) in normal subjects and group I increases during exercise, whereas that in group II decreases during exercise. LVEDP = left ventricular end-diastolic pressure.

A/E and the left ventricular end-diastolic pressure at rest in the 40 patients with old myocardial infarction. In 14 of the 40 patients (eight from group I and six from group II), left ventricular end-diastolic pressure was also measured during isometric handgrip exercise. The A/E ratio and left ventricular end-diastolic pressure increased significantly in group I (from 11 ± 3 to 13 ± 4 mm Hg). Conversely, despite a significantly greater increase in left ventricular end-diastolic pressure in group II (23 ± 3 to 30 ± 5 mm Hg) than that in

Figure 5. Change in the ratio of peak velocity in atrial contraction phase to peak velocity in early diastolic filling phase (ΔA/E) in each group. The ΔA/E in group I is significantly greater than that in the other groups, whereas ΔA/E in group II is smaller than that in the other groups. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.



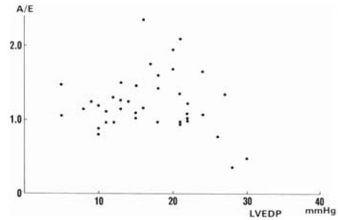


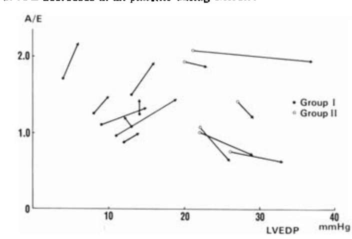
Figure 6. Relation between ratio of peak velocity in atrial contraction phase to peak velocity in early diastolic filling phase (A/E) and left ventricular end-diastolic pressure (LVEDP) at rest. There is no significant correlation between these two variables at rest in patients with old myocardial infarction.

group I, the A/E ratio decreased during exercise in all patients in group II.

Discussion

Previous studies. Doppler echocardiography is a simple noninvasive method for evaluating cardiac function in patients with coronary artery disease (1–3,6–8,19). Doppler-derived indexes are little influenced by left ventricular asynergy compared with values determined using cineangiography, radionuclide angiography or digitized M-mode echocardiography. Furthermore, the difference in mitral inflow velocity pattern appears to be related more to myocardial function and hemodynamic status than to disease type (16). Several investigators (5,13,14,16–18) have reported the relationship between the Doppler-derived inflow velocity pattern and left ventricular pressure. Kuecherer et

Figure 7. Changes in the ratio of peak velocity in atrial contraction phase to peak velocity in early diastolic filling phase (A/E) and left ventricular end-diastolic pressure (LVEDP) during exercise. The A/E increases with a slight increase in end-diastolic pressure in group I (closed circle). In group II (open circle), the change in end-diastolic pressure is significantly greater than that in group I, but A/E decreases in all patients during exercise.



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al. (14) observed that the Doppler-derived inflow velocity pattern was related to left ventricular filling pressure and, in patients with a high left ventricular end-diastolic pressure, the flow distribution showed predominantly early filling. Channer et al. (13) observed that left ventricular end-diastolic pressure could be estimated from the ratio of the areas of the two waveforms. However, these studies used only the Doppler velocity pattern at rest. In our study, the difference in response of the left ventricular inflow velocity pattern to isometric exercise was evaluated in patients with normal (<18 mm Hg) and elevated (≥18 mm Hg) left ventricular end-diastolic pressure.

A/E ratio and left ventricular end-diastolic pressure at rest. At rest, peak velocity of the E wave was lower, peak velocity of the A wave was higher and the A/E ratio was significantly higher in patients with myocardial infarction than those in the normal subjects, indicating that left ventricular diastolic function was impaired in both subgroups of myocardial infarction. However, A/E at rest was not related to left ventricular end-diastolic pressure: a wide range of pressures was obtained with the same A/E, indicating the difficulty in estimating left ventricular end-diastolic pressure from the Doppler inflow velocity pattern at a single point.

A/E and left ventricular end-diastolic pressure during isometric exercise. Isometric handgrip exercise testing increases blood pressure with only a moderate increase in heart rate, and this presents a simple and accurate approach to evaluating left ventricular performance in patients with coronary artery disease (20–28). In this study, the Doppler inflow velocity pattern and left ventricular end-diastolic pressure were evaluated during isometric handgrip exercise in patients with old myocardial infarction to elucidate the preload reserve in response to an acute increase in afterload. As a result, the A/E ratio increased significantly and left ventricular end-diastolic pressure remained at low level in group I, whereas despite a larger increase in left ventricular end-diastolic pressure, the A/E ratio decreased in all patients in group II. A new asynergic zone without clinical evidence of ischemia has been observed (22) to appear during handgrip exercise testing in patients with coronary artery disease. Ludbrook et al. (27) reported that asynchronous relaxation was exaggerated with the increased ventricular preload and afterload induced by isometric handgrip exercise.

Therefore, a decrease in peak velocity of the E wave and increase in peak velocity of the A wave indicates that impaired left ventricular relaxation progressed further during early diastole in response to acute increase in afterload in patients with normal left ventricular end-diastolic pressure (group I), but in the latter half of diastole, exaggerated atrial contraction worked effectively with a slight increase in preload. In contrast, left atrial filling pressure increased rapidly in response to an acute increase in afterload in patients with elevated left ventricular end-diastolic pressure (group II). Although elevated left atrial pressure increased early diastolic velocity, left ventricular pressure increased rapidly with left ventricular filling and, hence, the duration of filling in early diastole shortened and left ventricular diastolic filling volume decreased. In late diastole, a high left ventricular pressure disturbed the compensatory augmentation of atrial contraction, leading to a decrease in the late diastolic filling volume (29,30). Thus, in patients with a high left ventricular end-diastolic pressure, a compensatory mechanism could not have operated effectively with an acute increase in afterload due to a limited preload reserve.

Limitations. Two limitations of this study should be addressed. First, Doppler examination and cardiac catheterization were not performed simultaneously. However, left ventricular end-diastolic pressure was measured before any interventions such as coronary angiography and left ventriculography. Furthermore, left ventricular end-diastolic pressure measurement and Doppler examination were performed under the similar conditions, especially with similar heart rate and blood pressure (31). Second, Doppler examinations were performed by investigators who were blinded to cardiac catheterization data but were not blinded to the patient's prior status. With the guidance of a real-time two-dimensional color Doppler flow image, we believe that the smallest possible angle (<20°) between the transmitral inflow and the ultrasound beam was attained in all patients.

Clinical implications. Isometric and dynamic exercise are performed during routine daily activities. Therefore, in patients with old myocardial infarction, the hemodynamic alterations during isometric handgrip exercise testing should be evaluated to help manage their daily activities. The method described herein, which combines Doppler echocardiography and isometric handgrip exercise, is a useful, noninvasive means of predicting elevated left ventricular filling pressure and evaluating cardiac reserve.

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